REMARKS

Claim Amendments

Claims 1, 28, and 30 have been amended to delete the phrase "or a prodrug thereof." Claim 30 also has been amended to recite a method of reducing tumor formation by 50% in one year in an animal comprising administering to the animal about 0.1 to about 100 mg of a compound of Formula I per kg of body weight. This amendment is supported by the specification at, for example, page 11, lines 9-11, Example 2, and Figure 2. New claims 50-52 have been added and are supported by the specification at, for example, page 11, lines 9-11, Example 2, and Figure 2. No new matter has been added by way of these amendments.

The Pending Claims

Claims 1, 4-7, 9-20, 28, 30-34, 36-47, and 49-52 are pending. Claims 1, 28, 30, and 49 are currently being examined, whereas claims 4-7, 9-20, 31-34, and 36-47 are withdrawn. Applicants understand that, upon allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. § 1.141.

Summary of the Office Action

Claims 1, 28, 30, and 49 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description. Claims 1, 28, 30, and 49 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claims 1, 30, and 49 have been rejected under 35 U.S.C. § 102(e), as allegedly anticipated by Bernstein (U.S. Patent 5,840,734). Claims 28 and 30 have been rejected under the doctrine of obviousness-type double patenting in view of claim 22 of U.S. Patent 5,462,946 ("the '946 patent") and claim 2 of U.S. Patent 6,605,619 ("the '619 patent"). Reconsideration of the rejected claims is hereby requested.

Discussion of the Written Description Rejection

According to the Office Action, claims 1, 28, 30 and 49 encompass the use of "any prodrug," and therefore, the specification lacks proper written description of all prodrugs.

Claims 1, 28, and 30 have been amended to delete the phrase "or a prodrug thereof." Therefore, in view of these amendments, this rejection has been overcome.

The Office Action also contends that claim 28 lacks adequate written description in view of the term "tumor due to ataxia telangiectasia (AT) and Li-Fraumeni syndrome." Applicants respectfully disagree for the following reasons.

It is known to those skilled in the art that Li-Fraumeni syndrome is a cancer predisposition syndrome associated with soft-tissue sarcoma, breast cancer, leukemia, osteosarcoma, melanoma, and cancer of the colon, pancreas, adrenal cortex, and brain. See, for example, http://www.ghr.nlm.nih.gov/ghr/disease/lifraumenisyndrome#definition (printout enclosed). Furthermore, it is known in the literature that p53 null mice are good models for the human inherited cancer predisposition Li-Fraumeni syndrome. See, for example, Donehower, *Semin. Cancer Biol.*, 7(5): 269-278 (1996) (abstract enclosed).

As previously discussed, the Examples of the specification illustrate that the administration of a nitroxide of Formula (I) delayed the onset of all types of tumors that are typically associated with p53 gene defects. Moreover, specific cancers that are caused by a p53 mutation are well known in the literature. As stated previously on the record (see "Amendment and Response to Office Action" filed February 18, 2003), Hollstein et al. (*Science*, 253: 49-53 (1991)) reports that p53 mutations are common to cancers, including cancers of the colon, lung, esophagus, breast, liver, brain, reticuloendothelial tissue, and hematopoietic tissues (abstract enclosed).

It is further known to those skilled in the art that AT is an inherited genetic defect that predisposes humans to developing cancer (page 6, lines 16-21 of the present specification), particularly leukemia and lymphoma. See, for example, http://www.ninds.nih.gov/disorders/a_t/a-t.htm (printout enclosed). Researchers currently believe that cancer resulting from AT does not stem from a defect in the p53 gene. See, for example, Jonveaux, *Cancer Genet. Cytogenet.*, 66(2): 128-129 (1993) (abstract enclosed). However, as stated previously on the record, Applicants have shown the effectiveness of a nitroxide of Formula (I) (i.e., Tempol) in delaying the onset of tumor formation in *Atm*-deficient mice, which are models of AT.

In view of the foregoing, Applicants respectfully submit that the specification provides adequate written description for the claimed invention. One of ordinary skill in the art would know what cancers stem from the recited conditions, namely, AT and Li-Fraumeni syndrome. As a result, Applicants respectfully submit that this rejection has been overcome.

Discussion of the Indefiniteness Rejection

The Office Action contends that claims 1, 28, 30 and 49 are indefinite for the use of the term "prodrug." As discussed, claims 1, 28, and 30 have been amended to delete the phrase "or a prodrug thereof." Claim 49 is dependent upon claim 30. In view of the amendments, Applicants respectfully submit that the indefiniteness rejection has been overcome.

Discussion of the Anticipation Rejection

Claims 1, 30, and 49 allegedly are anticipated by Bernstein (U.S. Patent 5,840,734). Applicants note that the Office Action of September 18, 2002 cited Bernstein as a reference against then pending claims 1-3 and 22-27. In the "Amendment and Response to Office Action" filed by Applicants on February 18, 2003, it was argued that Bernstein should be removed as prior art. A Declaration under 37 C.F.R. § 1.131 by James B. Mitchell was submitted in support of the argument. The declaration established that Applicants conceived of and reduced to practice the invention prior to the publication date of Bernstein. A copy of the declaration is enclosed herewith. The Office Action dated July 16, 2003 indicated that the anticipation rejection of claims 1-3 and 22-27 over Bernstein would not be maintained in light of the Declaration. The declaration is also applicable to present claims 1, 30, and 49. Accordingly, the anticipation rejection should be removed. Further, Bernstein fails to disclose all the elements of claims 30 and 49, e.g., reduction of tumor formation by 50% in 1 year.

Discussion of the Obviousness-Type Double Patenting Rejection

Claims 28 and 30 have been rejected for obviousness-type double patenting in view of claim 22 of the '946 patent and claim 2 of the '619 patent. Claim 22 of the '946 patent recites a method for treating the effects of oxidative stress due to the production of harmful free radical species comprising administering a composition comprising Tempol to an

organism or biological material susceptible to oxidative stress. Claim 2 of the '619 patent recites a method of treating or preventing damage to normal cells, tissue, or organs in a mammal that has been exposed to ionizing radiation comprising administering to the mammal, after exposure to ionizing radiation, a composition comprising Tempol. According to the Office Action, the conflicting claims are not identical, but the prior methods of administering Tempol inherently possess the therapeutic effect of claims 28 and 30.

Pending claim 28 is directed to a method for delaying the onset of tumor formation or slowing the progression of a tumor due to AT or Li-Fraumeni syndrome. Both AT and Li-Fraumeni syndrome are rare *inherited* conditions. Li-Fraumeni syndrome also is a result of a p53 mutation. It cannot be said that practicing the method of claim 22 of the '946 patent (treating the effects of oxidative stress) or claim 2 of the '619 patent (treating or preventing damage to cells due to ionizing radiation) inherently results in delaying the onset of tumor formation or slowing the progression of a tumor due to these rare *inherited* genetic disorders. Inherency can be justified only when the missing descriptive is *necessarily* present in the cited reference. Probabilities and possibilities are insufficient to justify inherency. Treatment of oxidative stress or damage caused by ionizing radiation does not necessarily involve or suggest to those of ordinary skill in the art a method of delaying tumor formation due to AT or Li-Fraumeni syndrome. Thus, claim 28 is not obvious in view of these claims.

If the Office argues that, in view of the '946 patent and/or the '619 patent, the method of claim 28 is "obvious to try," Applicants respectfully submit, this is not the proper legal standard for determining obviousness (M.P.E.P. § 2145, X, B). In order to make a *prima facie* case of obviousness, claim 22 of the '946 patent and/or claim 2 of the '619 patent must *specifically* suggest the subject matter of claim 28. A *general* suggestion that Tempol may be cytotoxic to cancerous cells is insufficient as a basis for such a rejection. As a result of this general suggestion, one of ordinary skill in the art would be burdened with an undue amount of experimentation and testing to arrive at the method of claim 28. Further, nothing in the '946 patent and/or '619 patent indicates that a compound of Formula I may be useful for delaying the onset of tumor formation or slowing the progression of a tumor caused by a defect in the p53 and/or ATM gene, let alone a tumor due to AT or Li-Fraumeni syndrome. Therefore, the ordinarily skilled artisan would have no starting point in terms of genes to test and other factors.

Moreover, a declaration enclosed herewith by one of the inventors ("Second Declaration Under 37 C.F.R. § 1.132 of James B. Mitchell") describes how one of ordinary skill in the art would not have had a reasonable expectation of success to arrive at the invention of claim 28 based on claim 22 of the '946 patent and/or claim 2 of the '619 patent. As set forth in paragraph 7, Dr. Mitchell's declaration describes that to arrive at the presently claimed invention, one of ordinary skill in the art should test an untold number of gene mutations and study pathways relating to such mutations leading to cancer. This would entail undue experimentation and hardship.

Claim 30 has been amended to recite a method of reducing tumor formation by 50% in one year in an animal comprising administering to the animal about 0.1 to about 100 mg of a compound of Formula I per kg of body weight. Neither claim 22 of the '946 patent nor claim 2 of the '619 patent teach or suggest a method of reducing tumor formation by 50% in one year as recited in amended claim 30. Specifically, the '946 patent and the '619 patent do not identify the result effective variables recited in amended claim 30. In the absence of an identification of a result effective variable, there is no suggestive power in the cited references.

In view of the foregoing, claims 28 and 30 are not obvious in view of claim 22 of the '946 patent or claim 2 of the '619 patent. As such, the obviousness-type double patenting rejection should be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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